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(54) Title: USE OF PRAMIPEXOLE FOR THE TREATMENT OF ADDICTIVE DISORDERS

(57) Abstract: This patent application describes the treatment addictive disorders, psychoactive substance use disorders, intoxication disorders, inhalation disorders, alcohol addiction, tobacco addiction and/or nicotine addiction comprising administering a therapeutically effective, nontoxic dose of pramipexole and derivatives and or pharmaceutically acceptable salts thereof to a patient.

USE OF PRAMIPEXOLE FOR THE TREATMENT OF ADDICTIVE DISORDERS

FIELD OF THE INVENTION

The present invention relates to the use of pramipexole or 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzo-thiazole or the (-)-enantiomers thereof, and the pharmacologically acceptable salts thereof, for the treatment of several nervous system disorders, including: Addictive Disorders, Psychoactive Substance Use Disorders, Nicotine Addiction or Tobacco Addiction resulting in Smoking Cessation .

BACKGROUND OF THE INVENTION

Pramipexole is a dopamine-D_3/D_2 agonist the synthesis of which is described in European Patent 186 087 and its counterpart, U.S. Patent 4,886,812. It is known primarily for the treatment of schizophrenia and Parkinson's disease. German patent application DE 38 43 227 suggests pramipexole lowers the plasma level of prolactin. The English abstract of this case states that among the numerous pitutary gland related disorders that may be treated with pramipexole, it might be useful to treat illnesses caused by DA receptor blockage or DA secretion inhibition caused by medicaments. Further, it is known from German patent application DE 39 33 738 that pramipexole can be used to decrease abnormal high levels of thyroid stimulating hormone (TSH). U.S. patent 5,112,842 discloses the transdermal administration of the compounds and transdermal systems containing these active compounds. The WO patent application PCT/EP 93/03389 describes pramipexole as an antidepressant agent. PCT application PCT/US95/15618 discloses neuroprotective effects of pramipexole. US patent 5,001,861 describes the use of pramipexole for the treatment of Restless Legs Syndrome.

Scientists have also considered whether drugs like pramipexole might have useful properties to treat some forms of addiction. For example, see, A Carlsson, MF Piercey, Dopamine Receptor Subtypes in Neurological Psychiatric Diseases, *Clinical Neuropharmacology*, Vol. 18, Suppl. I, pp. S1-S5

(1995). RA Wise, D1- and D2-Type Contributions to Psychomotor Sensitization and Reward: Implications for Pharmacological Treatment Strategies, *Clinical Neuropharmacology*, Vol. 18, Suppl. I, pp. S-74-83 (1995). DCS Roberts, R Ranaldi, Effect of Dopaminergic Drugs on Cocaine Reinforcement, *Clinical Neuropharmacology*, Vol. 18, Suppl. I, pp. S84-S95 (1995). HD Kleber, Pharmacotherapy, Current and Potential, for the Treatment of Cocaine Dependence, *Clinical Neuropharmacology*, Vol. 18, Suppl. I, pp. S96-S109 (1995).

Here we disclose methods and dosages that explain how pramipexole can be used to treat specific addictive disorders.

SUMMARY OF THE INVENTION

The present invention particularly provides a method for the treatment of certain addictive disorders, such as pychoactive substance use disorders, nicotine addiction or tobacco addiction (with a result of smoking cessation or a decrease in smoking) comprising administering a therapeutically effective, nontoxic dose of pramipexole and derivatives and or pharmaceutically acceptable salts thereof to a patient suffering from or susceptible to such an addiction or disorder comprising the administration of an effective amount of pramipexole. By pramipexole is meant 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole, its (-)-enantiomer thereof, or (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)-benzothiazole and pharmacologically acceptable salts thereof especially (-)-2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole dihydrochloride (H_2O).

2-Amino-6-n-propyl-amino-4,5,6,7-tetrahydrobenzothiazole, particularly the (-)-enantiomer thereof, and the pharmacologically acceptable acid addition salts thereof can be given for treating the addictive disorders described here. The form of conventional preparations consist essentially of an inert pharmaceutical carrier and an effective dose of the active substance; e.g., plain or coated tablets, capsules, lozenges, powders, solutions, suspensions, emulsions, syrups, suppositories, etc.

Preferred are tablets containing the following amounts of active drug, in mg/tablet: 0.125, 0.25, 0.5, 1.0, 1.25 and 1.5 mg of pramipexole base (mg

pramipexole 2HCl), respectively, and further comprising mannitol, maize starch, colloidal silica, polividone and magnesium stearate as excipients. Preferred would be starting dose of 0.125 mg provided to a patient 3 times per day (tid). After accepting the starting dose, the patient may then seek to increase the dosage to a higher level with increases every 5 to 7 days up to a maximum dose of 10 mg/day, a preferred higher total daily dosage of about 6 mg/day with a more preferred highest dosage of about 4.5 to 5 mg/day.

For treating the addictive disorders described herein the drug may also be provided in chewable format, such as a chewing gum. The amount of active drug put in a chewable base may be half that suggested above, starting with about 0.075 mg per square of chewing gum being administered tid and followed with higher levels after the patient shows tolerance to the drug. Several chewing gum dosages are considered here including; 0.075, 0.10, 0.125, 0.150, in addition to those mentioned for a tablet. One or two chewing gum squares could be provided up to three times a day, depending on the therapeutic need of the patient.

Transdermal administration, such as with a skin patch application, and inhalation therapy, such as with an inhaler, is also foreseen where the patch or inhaler would deliver levels of pramipexole to the patient's blood in levels comparable to that suggested herein. A transdermal patch containing pramipexole could also be combined with a patch containing nicotine with the goal being the elimination of craving for tobacco containing products.

The drug is typically first administered to a patient at a low dosage to avoid possible nausea that may occur with higher starting doses. The dose is then titrated up to higher levels until a suitable therapeutic effect is acheived.

The effective dose range can be from 0.01 to 10.0 mg/day and patient, preferred is between 0.125 and 6 mg/day, more preferred between 0.375 to 5 mg/day and especially preferred is between 0.75 and 4.5 mg/day to a patient. In addition to being administered by oral or intravenous route pramipexole may also be administered transdermally or by inhalation.

Dosages should be typically increased gradually from a starting dose of about 0.125 mg of base drug given to the patient three times per day and

then increased every 5-7 days until optimal therapeutic effect is achieved. Providing patients do not experience intolerable side effects, the dosage should be titrated to achieve a maximal therapeutic effect. One ordinarily skilled in art of providing medicine, such as a physician or pharmacist should be able to determine the optimal dosage level after considering a patients age, size, medical history, responsiveness to and toleration for the drug.

DESCRIPTION OF THE DISORDERS THAT MAY BE TREATED WITH PRAMIPEXOLE

Addictive disorders and psychoactive substance use disorders, such as intoxication disorders, inhalation disorders, alcohol addiction, tobacco addiction and/or nicotine addiction. Tobacco and nicotine addiction would be treated with the goal of achieving either smoking cessation or smoking reductions.

Addictive disorders, alcohol and other psychoactive substance use disorders, disorders related to intoxication and inhalants and especially tobacco addiction or nicotine addiction, may be treated with pramipexole. Tobacco addiction or nicotine addiction would be treated with pramipexole in order to achieve smoking/chewing cessation or smoking/chewing reduction. General descriptions of addictive disorders, including disorders related to intoxication and inhalants and tobacco addiction or nicotine addiction may be found in many standard sources, such as, The American Psychiatric Press Textbook of Psychiatry, Second Edition, Edited by Robert E. Hales, Stuart C. Yudofsky, and John A. Talbott, copyright 1994, incorporated by reference, especially pp. 401 et. seq., section on "Nicotine" incorporated by reference. Another of many texts is the Manual of Psychiatric Therapeutics, Second Edition, edited by Richard I. Shader, incorporated by reference, especially pp. 85 from Chapter 11 (Hypnosis).

The treatment of alcohol and other psychoactive substance use disorders, such as disorders related to intoxication and inhalants and tobacco addiction or nicotine addiction but especially tobacco addiction involves the administration of pramipexole in a manner and form that provide a reduction in the symptoms of the disease. Tobacco addiction or nicotine

addiction in particular would be treated to achieve a reduction or cessation of smoking or chewing of nicotine containing materials by a patient. Cessation or a reduction in smoking or chewing of addictive or psychoactive substances involves the administration of pramipexole in a manner and form that provide a reduction in the symptoms of the disease, or with tobacco or nicotine with a reduction in the amount smoked or chewed. See the description above for methods and dosages for the proper administration of pramipexole for the treatment of these diseases and symptoms.

CLAIMS

1. A method of treating or enhancing the treatment of a disorder selected from, addictive disorders, psychoactive substance use disorders, intoxication disorders, inhalation disorders, alcohol addiction, tobacco addiction and or nicotine addiction comprising: administering a therapeutically effective, nontoxic dose of pramipexole, the compound 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole, its (-)-enantiomer thereof, or the administration of an effective amount, its dihydrochloride, or its dihydrochloride-(H_2O) and derivatives and or pharmaceutically acceptable salts thereof to a patient.

2. The method of claim 1 where pramipexole is used to treat or enhance the treatment of Tobacco and or Nicotine Addiction.

3. The method of claim 2 where pramipexole is used to reduce the craving for Tobacco or Nicotine containing products.

4. The method of claim 2 where pramipexole is used to reduce the smoking or chewing of Tobacco or Nicotine containing products.

5. The method of claim 1 wherein the dose of pramipexole is about 0.01-10.0 mg/day.

6. The method of claim 5 wherein the dose of pramipexole is about 0.125 - 6 mg/day.

7. The method of claim 6 wherein the dose of pramipexole begins at 0.125 mg administered to the patient 3 times a day and is then titrated to higher levels every 5 to 7 days until therapeutic effect is achieved.

8. A method for treating or enhancing the treatment of a disorder selected from:

addictive disorders, psychoactive substance use disorders, intoxication disorders, inhalation disorders, alcohol addiction, tobacco addiction and or nicotine addiction comprising administering a therapeutically effective, nontoxic dose of pramipexole and derivatives and or pharmaceutically acceptable salts thereof where the dose is either about 0.01-10.0 mg/day, about 0.125 - 6 mg/day, or about 0.375-5 mg/day or 0.75 to 4.5 mg/day to a patient in need of treatment of these disorders.

9. The use of pramipexole or its pharmaceutically acceptable salts in the manufacture of a medicament to treat: addictive disorders, psychoactive substance use disorders, intoxication disorders, inhalation disorders, alcohol addiction, tobacco addiction and or nicotine addiction where the medicament is in the form of: a tablet, where the tablet is in the size of a 0.125, 0.250, 0.50, 1.0, 1.25 or 1.5 mg tablet, a chewable form where the chewable form contains 0.075, 0.125, 0.250, 0.50 or 1.0 mg per square of chewable gum like substance; a transdermal patch; or an inhaler; where the patch or inhaler administers blood levels to the patient comparable to the tablets or gum described herein.

10 The method or use in claims 1-9 where the pramipexole dose range is about 0.125 to 4.5 mg. per patient per day.

11. The method or use in claims 1-9 where the pramipexole dose range is about 0.75 to 5 mg. per patient per day.

INTERNATIONAL SEARCH REPORT

Intl ional Application No
PCT/US 01/01232

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/425 A61P25/30 A61P25/34 A61P25/32 A61P25/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 01 22820 A (THE GENERAL HOSPITAL) 5 April 2001 (2001-04-05) the whole document ---	1,5,6, 8-11
X	EP 0 417 637 A (BOERINGER INGELHEIM KG) 20 March 1991 (1991-03-20) claims 1-4,6 page 3, line 18 - line 24 ---	1,5,6, 8-11
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Siatou, E

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Inte onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; AN: 127:171508, S. CAINE ET AL: "D3-receptor test in vitro predicts decreased cocaine self-administration in rats" XP002168920 & NeuroReport (1997), 8(9-10), 2373-2377 abstract	1
A	MAJ J ET AL: "THE BEHAVIOURAL EFFECTS OF PRAMIPEXOLE, A NOVEL DOPAMINE RECEPTOR AGONIST" EUROPEAN JOURNAL OF PHARMACOLOGY,NL,AMSTERDAM, vol. 324, no. 1, 1997, pages 31-37, XP000884558 ISSN: 0014-2999 abstract	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/US 01/01232

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WO 0122820 A	05-04-2001	NONE	
EP 417637 A	20-03-1991	DE 3930282 A	21-03-1991
		CA 2025003 A	12-03-1991
		DD 297557 A	16-01-1992
		HU 57584 A	30-12-1991
		IE 903278 A	10-04-1991
		JP 3106825 A	07-05-1991